BACKGROUND INFORMATION

FOR THE JOINT MEETING OF THE

MEDICAL IMAGING DRUGS ADVISORY COMMITTEE

AND THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
ABMT	autologous bone marrow transplant
ALL	acute lymphocytic leukemia
AML	acute myelogenous leukemia
AUC	area under the concentration-time curve
$AUC_{(0\text{-last})}$	area under the concentration-time curve from time 0 to the time of the last detectable concentration
CML	chronic myelogenous leukemia
CVB	cyclophosphamide/etoposide/BCNU
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
ARS	Acute Radiation Syndrome
ARS-HS	the Hematopoietic Syndrome of the Acute Radiation Syndrome
BARDA	Biomedical Advanced Research and Development Authority
BCNU	carmustine (1,3-bis-[2-chloroethyl]-1-nitroso-urea)
BEAM	BCNU/etoposide/cytosine arabinoside/melphalan
BID	twice daily
BLA	Biologics License Application
BMT	bone marrow transplant
CAE	cyclophosphamide/doxorubicin/etoposide
CBC	complete blood count
CFR	Code of Federal Regulations
cGy	centigray (unit of radiation)
CI	confidence interval
CL	serum clearance after IV administration
C_{max}	maximum observed concentration
CSF	colony-stimulating factor
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DLA	dog leukocyte antigen
DSN	duration of severe neutropenia
EPO	erythropoietin
FDA	Food and Drug Administration
FOIL	5-fluorouracil/leucovorin/oxaliplatin/irinotecan
FOLFIRI	5-fluorouracil/leucovorin/irinotecan

Abbreviation or Term	Definition/Explanation
FOLFOX4	5-fluorouracil/leucovorin/oxaliplatin
G-CSF	granulocyte colony-stimulating factor
G-CSFR	granulocyte colony-stimulating factor receptor
HD	Hodgkins disease
HIV	human immunodeficiency virus
IL	interleukin
IL-3	interleukin-3
IV	intravenous(ly)
LD	lethal dose
$LD_{x/y}$	lethal dose for x% of animals by day y
LGF	leukocyte growth factor
MGDF	macrophage-derived growth and development factor
MIDAC	Medical Imaging Drugs Advisory Committee
NIAID	National Institute of Allergy and Infectious Disease
NHL	non-Hodgkins lymphoma
ODAC	Oncologic Drugs Advisory Committee
PEG	polyethylene glycol
pre-IND	pre-Investigational New Drug (plan)
QD	once daily
REAC/TS	Radiation Emergency Assistance Center/Training Site
r-metHuG-CSF	recombinant methionyl human granulocyte colony-stimulating factor
RR	weighted summary relative risk
sBLA	supplemental Biologics License Application
SC	subcutaneous(ly)
SCN	severe chronic neutropenia
TBI	total body irradiation
$t_{1/2}$	half-life associated with the terminal phase
T_{max}	time at which maximum concentration was observed
US	United States
USPI	United States Prescribing Information
V_c	volume at the central compartment
WART	whole abdominal radiation therapy
WBC	white blood cell count

1. Executive Summary

Endogenous granulocyte colony-stimulating factor (G-CSF) is a lineage-specific colony-stimulating factor (CSF) that regulates the production of neutrophils within the bone marrow. It acts at all stages of neutrophil development, particularly the late stage, increasing the proliferation and differentiation of neutrophils from committed progenitor cells.

Neupogen (filgrastim) is a recombinant methionyl human G-CSF (r-metHuG-CSF) that acts on neutrophil precursors in the bone marrow in a manner consistent with endogenous G-CSF. The administration of Neupogen amplifies neutrophil production and decreases maturation time from 5-7 days to 1 day, leading to the rapid release of mature neutrophils from the bone marrow into the circulation. Neupogen requires daily injections to achieve therapeutic efficacy because of its short elimination half-life. Neulasta (pegfilgrastim), a pegylated form of Neupogen with sustained-duration of action, is administered only once per chemotherapy cycle.

In clinical trials in patients with cancer receiving myelosuppressive chemotherapy, Neupogen and Neulasta were shown to reduce the incidence and duration of severe neutropenia and therefore the associated febrile neutropenia. Both drugs were effective in accelerating neutrophil recovery and reducing the incidence of infections after myelosuppressive chemotherapy across chemotherapy regimens with a broad range (8% to 77%) of incidence of febrile neutropenia. In patients with cancer receiving such regimens, the use of Neupogen and Neulasta reduced the incidence of infections, hospital admissions for febrile neutropenia, use of intravenous anti-infectives, and the rates of infection-related mortality and early mortality (all cause mortality during the chemotherapy period).

The safety profiles of Neupogen and Neulasta have been well characterized through their clinical development programs and years of postmarketing experience (more than 20 years for Neupogen and more than 10 years for Neulasta). Most adverse experiences are related to the sequelae of the underlying malignancy or cytotoxic chemotherapy. Bone pain/pain in the extremity is the most commonly observed adverse reaction attributed to either product following cytotoxic chemotherapy in clinical studies.

Neupogen (administered daily at a dose of 5 µg/kg until an absolute neutrophil count [ANC] of 10 x 10^9/L post-nadir) and Neulasta (administered at a dose of 6 mg once per chemotherapy cycle) are approved in the United States (US) for use in patients receiving myelosuppressive anticancer drugs associated with a clinically significant risk of febrile

neutropenia. Neupogen is also approved in additional indications, including reducing the duration of neutropenia and neutropenia-related clinical sequelae, such as febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.

Amgen has had prior discussions with the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA) regarding the use of Neupogen and Neulasta in the setting of the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS) and supports the discussion at this Advisory Committee meeting by presenting the enclosed information regarding Neupogen and Neulasta to provide a context for the potential use of these products in ARS-HS.

Nonclinical data from studies in mice, beagles, and monkeys demonstrate reduced severity of myelosuppression with enhanced neutrophil recovery and improved survival after G-CSF treatment of animals exposed to lethal and sublethal doses of radiation.

Limited clinical trial and case study data are available in the literature regarding Neupogen administration in persons exposed to radiation; however, no conclusions can be drawn from this information.

Based on the underlying biology and limited animal studies, Amgen considers that Neupogen and Neulasta have the potential to provide clinical benefit as treatments for radiation-induced myelosuppression resulting from accidental radiation exposure.

2. Introduction

2.1 Objectives of this Briefing Document

The Joint Meeting of the Medical Imaging Drugs Advisory Committee (MIDAC) and the Oncologic Drugs Advisory Committee (ODAC) is being held on May 3, 2013 to discuss the safety and efficacy of currently approved leukocyte growth factors (LGFs) as potential treatments for radiation-induced myelosuppression associated with a radiological or nuclear incident. For this meeting, Amgen is providing a summary of the characteristics of Neupogen and Neulasta that are deemed relevant to the setting of the Hematopoietic Syndrome of the Acute Radiation Syndrome (ARS-HS).

This briefing document presents the pivotal clinical trial data that supported the approval of Neupogen and Neulasta for use in patients receiving myelosuppressive anticancer drugs associated with a clinically significant risk of febrile neutropenia and infection. Also described are clinical data supporting the use of Neupogen in stem cell transplantation (myeloablative and nonmyeloablative) therapy, nonclinical data from studies using granulocyte colony-stimulating factors (G-CSFs) in radiation-exposed animals, and an overview of literature case studies of colony-stimulating factor use in victims of radiological accidents.

2.2 Prior Interactions With US Governmental Agencies Regarding the Hematopoietic Syndrome of the Acute Radiation Syndrome

Amgen has had a number of interactions with various US governmental agencies, including the FDA and the Biomedical Advanced Research Development Authority (BARDA), regarding ARS-HS. Amgen recognizes the important public health issues involved and has sincere interest in understanding the potential use of Neupogen and Neulasta in the treatment of patients with ARS-HS. Beginning in 2002, Amgen was engaged in collaboration with the National Institutes of Health (NIH) Division of Allergy, Immunology, and Transplantation (DAIT) and National Institute of Allergy and Infectious Disease (NIAID) and participated in multiple interactions with the Food and Drug Administration (FDA) for guidance around a path forward to gain approval for Neupogen in ARS-HS through the animal rule cited in the Code of Federal Regulations (21 CFR 601, subpart H). Most recently, DAIT/NIAID/NIH in collaboration with Amgen submitted a pre-Investigational New Drug (pre-IND) plan on December 27, 2006. However, based on subsequent discussions, Amgen did not consider it feasible to pursue an approval at that time. This decision was due to a number of factors, including:

- Availability of laboratories capable of conducting animal studies with the same rigor as clinical efficacy studies (under 21 CFR 314.126)

- Accessibility of irradiation equipment and detailed methodology at the level required for clinical research
- Ability to provide adequate medical management of animals using the proposed protocol.
- Feasibility of establishing a clinical protocol adequate for collection of patient data to confirm safety and efficacy of Neupogen during the time of an emergency, as well as long term follow-up of patients receiving Neupogen post exposure to radiation.

No agreement was reached on a path forward with the FDA in 2007, and therefore Amgen did not pursue continued discussions with the FDA or the collaboration with DAIT/NIAID/NIH in the subsequent years. However, Amgen remains interested in addressing this potential public health need and supports the discussion at this Advisory Committee meeting by presenting the enclosed information regarding Neupogen and Neulasta to provide a context for the potential use of these products in ARS-HS.

2.3 Neupogen/Neulasta Approval History

Neupogen (filgrastim) was approved in 1991 to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. Neupogen has also been approved in the United States (US) for use in patients with acute myelogenous leukemia (AML) receiving induction or consolidation chemotherapy, patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT), the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis, and patients with severe chronic neutropenia (SCN). In addition to some of the indications noted above, Neupogen also has been approved in various countries outside of the US for patients with human immunodeficiency virus (HIV) infection and/or acquired immunodeficiency syndrome.

Neulasta (pegfilgrastim) was approved in the US on 31 January 2002 to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia. Neulasta also has been approved in various other countries for this indication.

Neupogen and Neulasta are each approved in over 100 countries worldwide.

2.4 Global Patient Exposure

Neupogen and Neulasta have been studied extensively in clinical trials. Since the initiation of Neupogen clinical trials in December 1986 through January 31, 2013, approximately 26,400 patients have been enrolled in Amgen-sponsored clinical trials, and as of January 31, 2013, approximately 8,876,000 patients worldwide have been treated with Neupogen in the postmarketing setting (Amgen data on file). Since the initiation of Neulasta clinical trials in September 1997 through January 31, 2013, approximately 5,400 patients have been enrolled in company-sponsored clinical trials, and as of January 31, 2013, approximately 4,350,000 patients worldwide have been treated with Neulasta in the postmarketing setting (Amgen data on file).

3. Neutropenia in Patients with Nonmyeloid Malignancies Receiving Myelosuppressive Anticancer Drugs

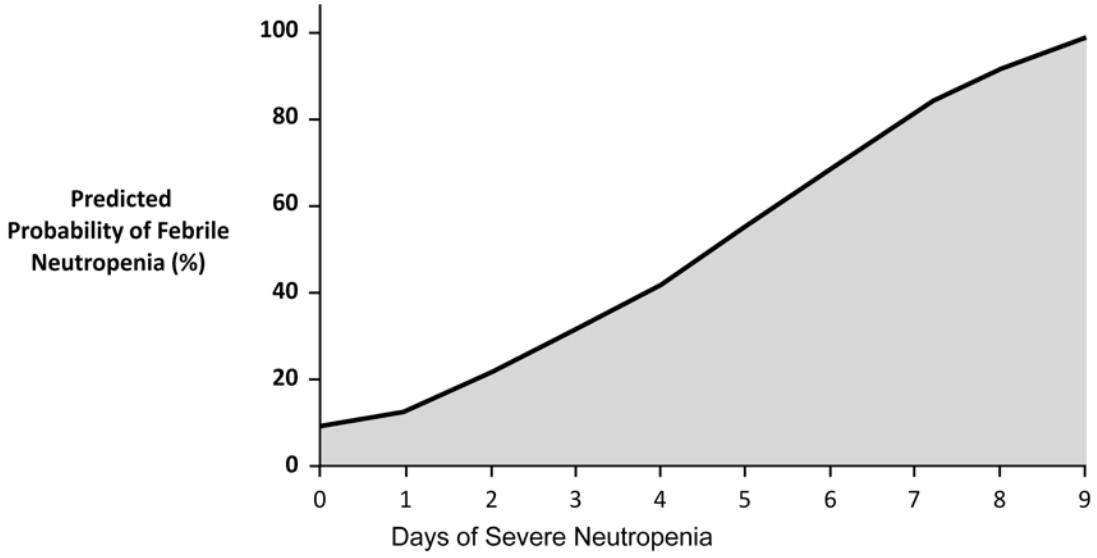
3.1 Disease State: Chemotherapy-induced Neutropenia and Febrile Neutropenia

The therapeutic utility of Neupogen and Neulasta in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy is evident when considering the consequences of severely reduced neutrophil concentrations in these patients, particularly the risk of infection.

Chemotherapy impacts rapidly dividing cells, including neutrophils, by directly causing cell death and slowing or stopping proliferation. Many chemotherapeutic agents produce myelosuppression as a side effect, and neutropenia (with related sequelae of life-threatening infections) is the most common serious side effect of myelosuppressive chemotherapy (hereinafter referred to as "chemotherapy-induced neutropenia") (Vogel et al, 2005; Crawford et al, 1991; Pettengell et al, 1992; Bodey et al, 1966). The risk of infection, as demonstrated by fever and neutropenia (febrile neutropenia), is related to the severity and duration of neutropenia (Blackwell and Crawford, 1994). While neutropenia is defined as a neutrophil count < 1.5 x 10^9/L (Hutchinson and Boxer, 1991), it is severe neutropenia (grade 3 [< 1.0 x 10^9/L]; grade 4 [< 0.5 x 10^9/L]) that has detrimental impact on patients. Febrile neutropenia as defined in the Common Terminology Criteria for Adverse Events (CTCAE) is fever (> 38°C) with grade 3 or 4 neutropenia (Cancer Therapy Evaluation program, CTCAE v 3.0, 2006).

In a study conducted in leukemia patients, the risk of infection increased substantially with decreasing neutrophil counts, and those patients with grade 3 neutropenia (neutrophil count < 1.0 x 10^9/L) for 1 week had more than a 50% incidence of fever and infection (Bodey et al, 1966). If the duration of neutropenia was prolonged, the risk of infection approached 100%. In a phase 3 study conducted in patients with small cell lung cancer treated with myelosuppressive chemotherapy, the occurrence of 6 days of grade 4 neutropenia (neutrophil count < 0.5 x 10^9/L) was associated with more than a 50% incidence of fever and infection (Crawford et al, 1991). A direct correlation was evident between infection as demonstrated by duration of grade 4 neutropenia and the predicted probability of febrile neutropenia (Figure 1) (Blackwell and Crawford, 1994). Together, these studies support a relationship of grade 3 or 4 neutropenia to febrile neutropenia and potentially serious infections.

Figure 1. Risk Model of Febrile Neutropenia Correlated With Duration of Grade 4 Neutropenia



Adapted from: Blackwell S, et al. Filgrastim (r-metHuG-CSF) in Clinical Practice. 1994.

Adapted from Blackwell and Crawford, 1994
The predicted probability of the development of febrile neutropenia (from a logistic regression model) is plotted by the days of neutropenia < 0.5 x 10^9/L

3.2 Impact of Severe Neutropenia and Febrile Neutropenia on Patients

Neutrophils are essential components in the prevention of infections. Prolonged periods of grade 3 or 4 neutropenia predispose patients to serious infections, which can lead to hospitalization and increased risk of death (Kuderer et al, 2006, Bodey et al, 1966).

Infection in the presence of febrile neutropenia is a medical emergency associated with significant morbidity and mortality. Patients with cancer who are hospitalized with febrile neutropenia may experience long hospital stays that involve administration of intravenous (IV) anti-infectives and are associated with a considerable mortality risk. A retrospective review using a hospital discharge database derived from 115 US medical centers was conducted to study all adult patients with cancer in that database who were hospitalized with febrile neutropenia between 1995 and 2000 (Kuderer et al, 2006). Among 41,779 patients with cancer hospitalized with febrile neutropenia, the average length of hospital stay was 11.5 days. The average length of stay varied by cancer type: among 22,142 of these patients with solid tumors and 8,703 patients with leukemia, the average length of stay was 8.1 days and 19.7 days, respectively. The corresponding in-hospital mortality among all patients, patients with solid tumors, and patients with leukemia was 9.5%, 8.0%, and 14.3%, respectively.

4. Neupogen and Neulasta

4.1 Biologic Structure, Function, and Mechanism of Action

Growth factors support the survival and differentiation of hematopoietic cells. Endogenous granulocyte colony-stimulating factor (G-CSF) is a lineage-specific colony-stimulating factor (Demetri and Griffin, 1991). It acts at all stages of neutrophil development, particularly the late stage, increasing the proliferation and differentiation of neutrophils from committed progenitor cells. G-CSF also enhances the survival and function of mature neutrophils by increasing phagocytic activity, antimicrobial killing, and antibody-dependent cell-mediated cytotoxicity (Bociek and Armitage, 1996).

4.1.1 Neupogen

Neupogen (filgrastim) is a recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF); it is a 175-amino acid protein with a molecular weight of 18.8 kilodaltons (kD). The biological activities of Neupogen are identical to those of endogenous G-CSF.

Neupogen stimulates stem cells to divide and progressively differentiate into myeloblasts and myelocytes, which ultimately develop into neutrophils, forming the first line of defense against infection (Jandl 1996; Nuñez and Brady, 1997). The administration of Neupogen as per the approved label (Section 4.6.1) amplifies neutrophil production (greater cell numbers are produced relative to endogenous G-CSF) and decreases maturation time from 5 days to 1 day, leading to the rapid release of mature neutrophils from the bone marrow into the circulation (Kim and Demetri, 1996).

4.1.2 Neulasta

Neulasta (pegfilgrastim) is a pegylated form of Neupogen, with sustained duration of action. Neulasta consists of the Neupogen molecule bound to a 20-kD monomethoxypolyethylene glycol (PEG) molecule, such that the molecular weight of Neulasta is approximately 39 kD (Molineux et al, 1999). The biologic activity and mechanism of action of Neulasta are identical to those of Neupogen (Molineux, 2004).

4.2 Pharmacokinetics in Humans

4.2.1 Neupogen

The pharmacokinetics of Neupogen in humans exhibit nonlinear characteristics after IV and subcutaneous (SC) administration. The clearance of Neupogen has been attributed to neutrophil-mediated clearance, presumably involving G-CSF receptors (G-CSFR) on neutrophils and neutrophil precursors. It is believed that Neupogen, after binding to G-CSFR, is internalized and degraded inside the cells. Serum concentrations of

Neupogen have been shown to be inversely correlated with the number of circulating neutrophils. In addition to neutrophil-mediated clearance, renal clearance plays an important role in the elimination of Neupogen. The drug, which has a molecular weight of 18.8 kD, is readily filtered at the renal glomerulus and subsequently reabsorbed and metabolized to amino acids in the proximal tubules (Yang and Kido, 2011). After SC administration of Neupogen to healthy volunteers and patients with cancer, the Neupogen concentration reaches a maximum within 2 to 8 hours and subsequently declines with a terminal half-life of approximately 3.5 hours (Neupogen United States Prescribing Information [USPI]). Because of its short elimination half-life, daily injections of Neupogen are required to maintain the therapeutic effect.

4.2.2 Neulasta

After SC administration, Neulasta is absorbed to the systemic circulation slower than Neupogen; therefore, the Neulasta concentrations reach a maximum at approximately 24 hours after dosing. Neulasta is engineered for slow elimination through reduction of renal clearance. Results from a phase 1 clinical study showed that the serum concentration and absolute neutrophil count (ANC) profiles over time of Neulasta were similar across the groups with various degrees of renal function, suggesting that the kidney plays a very minor role in the elimination of Neulasta. It is believed that the PEG moiety makes the hydrodynamic radius of Neulasta too large to be filtered by the glomerulus (Yang and Kido, 2011). As such, neutrophil-mediated clearance is the predominant pathway in the elimination of Neulasta, which renders a very efficient self-regulating clearance mechanism. That is, Neulasta increases the production of neutrophils and neutrophil precursors, which in turn clear the drug from the circulation. This complex pharmacokinetic-pharmacodynamic relationship results in sustained duration of action of Neulasta compared with Neupogen. The terminal half-life of Neulasta is approximately 15 to 80 hours in patients with cancer (Neulasta USPI).

4.3 Key Clinical Efficacy Data for Neupogen and Neulasta

The safety and efficacy of Neupogen and Neulasta in decreasing the risk of febrile neutropenia and its sequelae have been established in robust clinical trials and have been continuously monitored in worldwide postmarketing experience (> 20 years for Neupogen and > 10 years for Neulasta). Decreasing the incidence of infection, as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs is of relevance to the setting of significant and unexpected radiation exposure.

4.3.1 Neupogen

In two phase 3, double-blind, placebo-controlled clinical trials, one supporting the US regulatory approval (Crawford et al, 1991) and the other providing additional support for the EU regulatory approval (Trillet-Lenoir et al, 1993), Neupogen reduced the depth and duration of the neutrophil nadir in patients with small cell lung cancer treated with myelosuppressive chemotherapy (Table 1). In these studies, 341 patients with small cell lung cancer were randomized to receive daily SC Neupogen (230 µg/m^2) or placebo beginning on day 4 of each chemotherapy (cyclophosphamide/doxorubicin/etoposide [CAE]) cycle. In these studies, Neupogen was shown to reduce the incidence and duration of severe neutropenia and associated febrile neutropenia (temperature ≥ 38.2°C with ANC < 1.0 x 10^9/L [eg, grade 3 or 4 neutropenia]) and the duration of severe (grade 4) neutropenia in patients receiving myelosuppressive chemotherapy. Similar effects were seen in patients with acute AML (Heil et al, 1997), in which 521 patients with AML were randomized to receive daily SC Neupogen (5 µg/kg/day) or placebo after standard induction and consolidation therapy (Table 2).

In these and other studies in patients with cancer receiving myelosuppressive chemotherapy, the use of Neupogen also reduced the incidence of infections, hospital admissions for febrile neutropenia, and use of IV anti-infectives (Morstyn et al, 1994). For example, in one study, the incidence of hospitalization was 69% for placebo-treated patients in cycle 1 versus 52% for Neupogen-treated patients (P = 0.032). The incidence of antibiotic usage in this study was 60% for placebo-treated patients in cycle 1 versus 38% for Neupogen-treated patients (P = 0.003) (Crawford et al, 1991).

Table 1. Effects of Neupogen on Duration of Severe Neutropenia and Incidence of Febrile Neutropenia in Placebo-controlled Clinical Trials: Pivotal Trials in Patients With Small Cell Lung Cancer

Study	Tumor	Chemotherapy	Neupogen Dose	Febrile Neutropenia[c]		Median Duration of Severe Neutropenia[d]	
				Neupogen	Placebo	Neupogen	Placebo
Crawford et al (1991)[a] N = 211	SCLC	CAE	230 µg/m^2	28% (cycle 1)	57% (cycle 1) P < 0.001	3 days (cycle 1)	6 days (cycle 1) P < 0.001
				40% (across cycles)	77% (across cycles) 95% CI: 1.5%, 2.5% P < 0.001	1 day (across cycles)	6 days (across cycles) P < 0.005
Trillet-Lenoir et al (1993)[b] N = 130	SCLC	CAE	230 µg/m^2	20% (cycle 1)	41% (cycle 1) P < 0.012	Range < 1 day to 3 days (by cycle)	Range 9 days to 11 days (by cycle) P < 0.001
				26% (across cycles)	53% (across cycles) P < 0.002		

ANC =absolute neutrophil count; SCLC = small cell lung cancer; 95% CI = 95% confidence interval for difference
CAE = cyclophosphamide/doxorubicin/etoposide;
[a] US registrational trial
[b] EU registrational trial
[c] Febrile neutropenia definition for Crawford et al; Trillet-Lenoir et al: ANC < 1.0 x 10^9/L and temperature ≥ 38.2^{0}C
[d] Severe Neutropenia definition by study:
Crawford et al: grade 4
Trillet-Lenoir et al: grade 3 and 4

Table 2. Effects of Neupogen on Duration of Severe Neutropenia and Incidence of Febrile Neutropenia in Placebo-controlled Clinical Trials: Patients With Acute Myelogenous Leukemia

Study	Tumor	Chemotherapy	Neupogen Dose	Febrile Neutropenia[a]		Median Duration of Severe Neutropenia[b]	
				Neupogen	Placebo	Neupogen	Placebo
Heil et al (1997)	AML	DAV (Induction 1 and 2, Consolidation 1, Consolidation 2 [DAV]); HD-Ara-C/DNR (Consolidation 2 [HD-Ara-C/DNR])	5 µg/kg/day	78%[c]	72%[c] P = 0.34	10.0 days[c]	14.0 days[c] P = 0.015
N = 521				32%[d]	47%[d] P = 0.007	4.0 days[d]	11.0 days[d] P = 0.0001
				27%[e]	53%[e] P = 0.003	5.0 days[e]	10.0 days[e] P = 0.0001
				90%[f]	88%[f] P = 0.82	13.0 days[f]	18.5 days[f] P = 0.001

AML = acute myelogenous leukemia; ANC =absolute neutrophil count;
DAV = daunorubicin/cytosine arabinoside/etoposide (induction 1 and induction 2, consolidation 1, and consolidation 2 [DAV]); HD-Ara C/DNR = high dose cytosine arabinoside/daunorubicin (consolidation 2 [HD-AraC/DNR])

[a] Febrile neutropenia definition: an oral temperature ≥:38.0°C on the same day that the ANC was < 0.5 x 10^9/L
[b] Severe Neutropenia definition: grade 4;
[c] Induction 2 phase
[d] Consolidation 1 phase
[e] Consolidation 2 (DAV) phase
[f] Consolidation 2 (HD-Ara-C/DNR) phase

4.3.2 Neulasta

Two phase 3, double-blind, active- (Neupogen-) controlled non-inferiority clinical trials supported the US regulatory approval of Neulasta (Holmes et al, 2002; Green et al, 2003). In these studies, a total of 467 patients with breast cancer were randomized to receive a single SC injection of Neulasta (6 mg) on day 2 or daily SC Neupogen (5 µg/kg/day) beginning on day 2 of each chemotherapy (doxorubicin/docetaxel) cycle. Neulasta was non-inferior in reducing the incidence and duration of severe neutropenia and the associated incidence of febrile neutropenia (Table 3) (Neulasta USPI). Neulasta also reduced the incidence of febrile neutropenia in a phase 3 placebo-controlled clinical trial conducted to support a supplemental BLA (sBLA) (Vogel et al, 2005) (Table 4), in which 928 patients with breast cancer were randomized to receive a single SC injection of Neulasta (6 mg) or placebo on day 2 of each chemotherapy (docetaxel) cycle. Outcomes consistent with these effects on febrile neutropenia were seen in a study in subjects with colorectal cancer, in which 241 patients were randomized to receive a single SC injection of Neulasta (6 mg) or placebo 24 hours after completion of chemotherapy (ie, on day 4) of each chemotherapy cycle (5-fluorouracil/leucovorin/oxaliplatin [FOLFOX4] , 5-fluorouracil/leucovorin/irinotecan [FOLFIRI], or 5-fluorouracil/leucovorin/oxaliplatin/irinotecan] [FOIL]) (Hecht et al, 2010) (Table 4) and in a study in patients with non-Hodgkins lymphoma (NHL) (Vose et al, 2003), in which 66 patients were randomized to receive a single SC injection of Neulasta (100 µg/kg) on day 2 or daily SC Neupogen (5 µg/kg/day) beginning on day 2 of each chemotherapy cycle (etoposide/methylprednisolone/cisplatin/cytarabine [ESHAP]) (Table 5).

In these and other studies in patients with cancer receiving myelosuppressive chemotherapy, the use of Neulasta significantly reduced the incidence of infections, hospitalizations for febrile neutropenia, and antibiotic use. For example, in one study, patients who received Neulasta had a 1% incidence of hospitalizations and a 2% incidence of IV anti-infective use, compared with 14% and 10%, respectively, for patients who received placebo (Vogel et al, 2005).

Table 3. Effects of Neulasta on Duration of Severe Neutropenia and Incidence of Febrile Neutropenia in Active- (Neupogen-) controlled Clinical Trials: Pivotal Trials in Patients With Breast Cancer

Study	Tumor	Chemotherapy	Neulasta Dose	Febrile Neutropenia[b] Across Cycles		Mean Duration of Grade 4 Neutropenia in Cycle 1	
				Neulasta	Neupogen	Neulasta	Neupogen
Holmes et al (2002)[a] N =310	Breast Cancer	AT	100 µg/kg	9%	18%[c] P = 0.029 95%CI: -17%, -1%	1.7 days	1.8 days
Green et al (2003)[a] N =157	Breast Cancer	AT	6 mg	13%	20%[c] P = NS 95%CI: -19%, 5%	1.8 days	1.6 days

AT = doxorubicin/docetaxel; NS = not statistically significant
[a] US registrational trial
[b] Febrile neutropenia: ANC < 0.5 x 10^9/L with a coincidental oral equivalent temperature ≥ 38.2^{0}C
[c] The febrile neutropenia rates are similar for Neulasta and Neupogen in this noninferiority trial.

Table 4. Effects of Neulasta on Incidence of Febrile Neutropenia in Placebo-controlled Clinical Trials: Patients With Breast Cancer or Colorectal Cancer

Study	Tumor	Chemotherapy	Neulasta Dose	Febrile Neutropenia[b] Across Cycles	
				Neulasta	Placebo
Vogel et al (2005)[a] N =928	Breast Cancer	Docetaxel	6 mg	1%	17% P < 0.001
Hecht et al (2010) N = 241	Colorectal Cancer	FOLFOX 4, FOLFIRI, or FOIL	6 mg	2%	8% P = 0.04

ANC = absolute neutrophil count; sBLA = supplemental biologics license application; USPI = United States Prescribing Information
Note: Duration of severe neutropenia was not determined in these studies.
5-FU = 5-fluorouracil; FOIL = 5-FU/leucovorin/oxaliplatin/irinotecan ; FOLFIRI = 5-FU/leucovorin/irinotecan; FOLFOX4 = 5-FU/leucovorin/oxaliplatin
[a] US sBLA pivotal trial, to support adding 20% febrile neutropenia to the USPI,
[b] Febrile neutropenia definition by study:
Vogel et al: temperature ≥38.2^{0}C and neutrophil count <0.5 x 10^9/L on the same day as fever or the day after
Hecht et al: Grade 3 and 4 febrile neutropenia – temperature ≥38.2^{0}C and ANC < 1.0 x 10^9/L on the same day as fever or the day after

Table 5. Effects of Neulasta on Duration of Severe Neutropenia and Incidence of Febrile Neutropenia in Active- (Neupogen-) controlled Clinical Trials: Patients With Non-Hodgkins Lymphoma or Acute Myelogenous Leukemia

Study	Tumor	Chemotherapy	Neulasta Dose	Febrile Neutropenia[a] Across Cycles[c]		Mean Duration of Grade 4 Neutropenia in Cycle 1	
				Neulasta	Neupogen		
Vose et al (2003) N = 66	NHL	ESHAP	100 µg/kg	21%	19%[b] P = NS 95%CI: -19%, 22%	2.8 days	2.4 days

ANC = absolute neutrophil count; NHL = non-Hodgkins lymphoma; NS = not significant; 95% CI = 95% confidence interval for difference
ESHAP = etoposide/methylprednisolone/cisplatin/cytarabine
[a] Febrile neutropenia definition: ANC < 0.5×10^9/L and temperature ≥ 38.2^0
[b] The febrile neutropenia rates are similar for Neulasta and Neupogen in this noninferiority trial.
[c] Across cycles 1 and 2 (small numbers of patients received treatment in cycles 3 and 4)

4.3.3 Summary of Neupogen and Neulasta Clinical Efficacy

Neupogen and Neulasta are similar in their efficacy to reduce the incidence and duration of severe neutropenia and the incidence of febrile neutropenia when administered per label dose and duration in registrational clinical trials (see Table 1, Table 2, Table 3, and Table 4). Of note, considering placebo-controlled trials, Neupogen and Neulasta reduced neutropenia incidence and severity across chemotherapy regimens with a broad range (8% to 77%) of incidence of febrile neutropenia (Table 1, Table 2, Table 4).

4.4 Summary of Neupogen and Neulasta Safety Data

The safety profiles of Neupogen and Neulasta are well characterized through their clinical development programs and years of postmarketing experience (20 years for Neupogen and over 10 years for Neulasta). The safety profiles in the chemotherapy-induced neutropenia indication are generally similar between the two products, with bone pain being the only commonly observed adverse event.

4.4.1 Neupogen

In clinical trials involving more than 350 patients receiving Neupogen following nonmyeloablative cytotoxic chemotherapy, most adverse experiences were related to the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase 2 and 3 trials, medullary bone pain, reported in 24% of patients, was the only consistently observed adverse reaction attributed to Neupogen therapy. This bone pain was generally reported to be of mild-to-moderate severity and was managed in most patients with non-narcotic analgesics (Neupogen USPI, under Clinical Trial Experience [chemotherapy-induced neutropenia]). Leukocytosis (white blood cell count [WBC] > 100 $x10^9$/L) was observed in approximately 2% of patients receiving Neupogen at doses above 5 µg/kg/day, with no reports of adverse events associated with this degree of leukocytosis. In a randomized, double-blind, placebo-controlled trial of Neupogen therapy after combination chemotherapy in patients (N = 207) with small cell lung cancer, skeletal pain was the only adverse event with a frequency greater in the Neupogen group than the placebo group, and the other adverse events were consistent with those observed in patients with cancer receiving cytotoxic chemotherapy.

In a randomized phase 3, placebo-controlled clinical trial in patients with AML receiving Neupogen postchemotherapy, adverse events reported with a frequency > 5% included petechiae, epistaxis, and transfusion reactions. Overall, the frequency of all reported adverse events was similar in both the Neupogen and placebo groups.

In clinical trials of patients with cancer receiving bone marrow transplantation, the reported adverse events were those typically seen in patients following intensive chemotherapy followed by bone marrow transplant. The most common events reported in both control and Neupogen treatment groups included stomatitis, nausea, and vomiting, generally of mild to moderate severity, and were considered unrelated to Neupogen.

Warnings described in the Neupogen USPI that are relevant to patients with cancer receiving myelosuppressive chemotherapy comprise allergic-type reactions (including anaphylaxis), splenic rupture (very rarely reported), acute respiratory distress syndrome (ARDS), alveolar hemorrhage and hemoptysis, sickle cell crises in patients with sickle cell disorders, cutaneous vasculitis, and thrombocytopenia. Precautions in the USPI include simultaneous use with cytotoxic chemotherapy (24 hours before through 24 after administration) or with radiation therapy, leukocytosis in patients with cancer receiving myelosuppressive chemotherapy, immunogenicity potential, cutaneous vasculitis, and potential effects on malignant cells. The possibility that Neupogen can act as a growth factor for any tumor type cannot be excluded.

4.4.2 Neulasta

In a placebo-controlled clinical trial in patients receiving Neulasta following nonmyeloablative cytotoxic chemotherapy, the most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the Neulasta group were bone pain and pain in the extremity (Neulasta USPI). Leukocytosis was observed with a frequency of < 1%, and no complications attributable to leukocytosis were reported.

Warnings described in the Neulasta USPI include peripheral blood progenitor cell mobilization use, splenic rupture, ARDS, allergic-type reactions, and sickle cell crises in patients with sickle cell disorders. Precautions in the USPI include simultaneous use with chemotherapy or radiation therapy and potential effects on malignant cells. The possibility that pegfilgrastim can act as a growth factor for any tumor type cannot be excluded.

4.5 Reduction in Mortality

Published reports suggest that primary prophylaxis with G-CSF support, including Neupogen or Neulasta, reduce the risk of mortality in adult patients with cancer. Individual studies were not designed to determine any effects on mortality rate and, where data from Neupogen phase 3 studies were collected and analyzed for mortality

(see Section 4.3 and Section 5), there were no significant differences compared with placebo (Neupogen USPI). However, when data across several clinical studies were examined by meta-analysis, Neupogen and Neulasta and other CSFs were shown to reduce the risk of infection-related mortality and early mortality (all cause mortality during the chemotherapy period). For example, in a retrospective analysis of 3,493 adult patients with cancer receiving chemotherapy for solid tumors or malignant lymphoma in 17 randomized controlled clinical trials studying G-CSF administration in the first cycle of chemotherapy before the onset of neutropenia, G-CSFs reduced infection-related mortality and early mortality (Kuderer et al, 2007) (Table 6).

Table 6. Mortality Data From Retrospective Analysis of 17 Randomized, Controlled Clinical Studies

	% Mortality (RR)[b]	
	Control	All G-CSF
Infection-related Mortality	2.8%	1.5% (0.55 [95% CI, 0.34-0.90]) P = 0.018
Early Mortality[a]	5.7%	3.4% (0.60 [95% CI, 0.43-0.83]) P = 0.002

Adapted from : Kuderer et al, 2007
CI = confidence interval; G-CSF = granulocyte colony-stimulating factor
[a] All cause mortality during the chemotherapy period
[b] RR = weighted summary relative risk

4.6 Approved Dose, Duration, and Regimen

The approved doses and durations summarized below from the respective USPIs are supported by the efficacy, safety, and pharmacokinetic characteristics observed in the Neupogen and Neulasta registrational clinical trials.

4.6.1 Neupogen

Based on the US registrational trial, the labeled recommended starting dose of Neupogen in patients with cancer receiving myelosuppressive therapy is 5 µg/kg/day, administered as a single daily injection by SC bolus injection, by short IV infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion. A complete blood count (CBC) and platelet count should be obtained before instituting Neupogen therapy and monitored twice weekly during therapy. Doses may be increased in increments of 5 µg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir.

Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic therapy, Neupogen should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. Neupogen should not be administered in the period 24 hours before the administration of chemotherapy. Neupogen should be administered daily for up to 2 weeks, until the ANC has reached 10 x 10^9/L following the expected chemotherapy-induced neutrophil nadir. The duration of Neupogen therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Neupogen therapy should be discontinued if the ANC surpasses 10 x 10^9/L after the expected chemotherapy-induced neutrophil nadir. In phase 3 trials, efficacy was observed at doses of 4 to 8 µg/kg/day.

4.6.2 Neulasta

Based on the US registrational trials, the labeled recommended adult dosage is a single SC injection of 6 mg administered once per chemotherapy cycle. Neulasta is not to be administered between 14 days before and 24 hours after administration of cytotoxic chemotherapy.

4.7 Use in Specific Patient Populations

Administration of Neupogen or Neulasta in certain populations of patients may require additional considerations, as described in the respective USPIs and summarized below.

4.7.1 Neupogen

Specific populations studied in Neupogen registrational trials described in the Neupogen USPI include geriatric patients, pediatric patients, pregnant women, and nursing women. Use of Neupogen in these populations per the USPI is summarized in Table 7.

4.7.2 Neulasta

Specific populations studied in Neulasta registrational trials and described in the Neulasta USPI include gender specificity, geriatric patients, patients with renal dysfunction, pregnant women, and nursing women. Use of Neupogen in these populations is summarized in Table 7.

Table 7. Use of Neupogen and Neulasta in Specific Populations

Population	Neupogen	Neulasta
Gender specificity	Not described in USPI	No gender-related differences were observed in the pharmacokinetics of Neulasta
Geriatric subjects (≥ 65 years of age)	No difference in safety or effectiveness compared with younger subjects[a]	No differences in the pharmacokinetics of geriatric patients (≥ 65 years of age) compared with younger patients
Pediatric subjects	No adverse effects on height or weight; no alteration in sexual maturation or endocrine function[b] Well tolerated in the cancer setting; musculoskeletal pain was the only consistently reported adverse event. Among 12 pediatric patients with neuroblastoma who received up to 6 cycles of cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with Neupogen, there was one report of palpable splenomegaly. The occurrence of musculoskeletal pain was no different from the experience in the adult population.	Per the USPI, the safety and effectiveness of Neulasta for pediatric use has not been established. The 6 mg fixed dose single-use syringe formulation should not be used for infants, children, or smaller adolescents (< 45 kg). In a multicenter, randomized, open-label study of a single SC Neulasta injection (100 µg/kg) compared with daily SC Neupogen administration (5 µg/kg) in 44 pediatric patients (stratified into 3 age groups [0-5, 6-11, and 12-21 years]) receiving myelosuppressive chemotherapy for sarcoma after chemotherapy, Neulasta and Neupogen were similar for all efficacy and safety end points, and their pharmacokinetic profiles were consistent with those in adults (Spunt et al, 2010). Efficacy endpoints included duration of severe (grade 4) neutropenia in chemotherapy cycles 1 and 3, rates of febrile neutropenia, and time to ANC recovery > 0.5 x 10^9/L in cycles 1 and 3. Younger children experienced more protracted neutropenia and had higher median pegfilgrastim exposure than older children.

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ANC = absolute neutrophil count; SC = subcutaneous; USPI = United States Prescribing Information
Except where otherwise noted, information in this table is based on the Neupogen USPI and the Neulasta USPI.
[a] among 855 subjects enrolled in 3 randomized, placebo-controlled trials of Neupogen use to decrease the risk of febrile neutropenia
[b] height/weight: long-term follow-up of postmarketing surveillance study; sexual maturation/endocrine function: limited data from patients followed from a phase 3 study up to 1.5 years
[c] in a study of 30 subjects with varying degrees of renal dysfunction including end-stage renal disease
[d] based on animal data and the lack of adequate and well-controlled studies in pregnant women

Table 7. Use of Neupogen and Neulasta in Specific Populations

Population	Neupogen	Neulasta
Renal dysfunction	Not described in USPI	Renal dysfunction had no effect on the pharmacokinetics of Neulasta[c]; thus, dose adjustment in patients with renal dysfunction is not necessary
Pregnancy	Neupogen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus[d] (Pregnancy Category C)	Neulasta should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus[d] (Pregnancy Category C)
Nursing women	It is not known whether Neupogen is excreted in human milk. Caution should be exercised if Neupogen is administered to nursing women.	It is not known whether Neulasta is excreted in human milk. Caution should be exercised if Neulasta is administered to nursing women.

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ANC = absolute neutrophil count; SC = subcutaneous; USPI = United States Prescribing Information
Except where otherwise noted, information in this table is based on the Neupogen USPI and the Neulasta USPI.
[a] among 855 subjects enrolled in 3 randomized, placebo-controlled trials of Neupogen use to decrease the risk of febrile neutropenia
[b] height/weight: long-term follow-up of postmarketing surveillance study; sexual maturation/endocrine function: limited data from patients followed from a phase 3 study up to 1.5 years
[c] in a study of 30 subjects with varying degrees of renal dysfunction including end-stage renal disease
[d] based on animal data and the lack of adequate and well-controlled studies in pregnant women

5. G-CSFs in Stem Cell Transplantation

Autologous bone marrow transplantation (ABMT) after myeloablative chemotherapy provides a hematopoietic stem cell source to help restore marrow function. Autologous BMT produces a hematologic syndrome characterized by pancytopenia, predisposing patients to increased risk of infection and sepsis (DiCarlo et al, 2011, Dainiak, 2010, Weisdorf et al, 2006). As a result, patients undergoing autologous BMT require G-CSFs to mitigate the risk of infection-related complications. Since both autologous BMT and ARS-HS share a common path of immune suppression and responsiveness to G-CSF, autologous BMT may contribute in part to an understanding of the hematologic manifestations of ARS-HS.

Survival of patients after marrow transplantation depends on the prompt functioning of hematopoietic grafts, and the use of G-CSFs has been shown to stimulate hematopoietic recovery in patients following radiation containing conditioning regimens (Storb et al, 1997). Nonclinical studies using non-ablative radiation in dogs have demonstrated that G-CSF with immunosuppressants helped achieve stable engraftment and stable hematopoietic chimerism after marrow transplantation in dog leukocyte antigen- (DLA-) identical littermate dogs exposed to 450 cGy of total body irradiation (TBI) (Storb et al, 1999; Storb et al, 1997; Yu et al, 1995). These findings are consistent with G-CSF use to improve bone marrow engraftment and survival.

Given the highly myelosuppressive nature of the chemotherapy necessary for BMT, Amgen studied higher doses of Neupogen (10 to 30 µg/kg/day) in phase 3, randomized, controlled BMT studies supporting the approval of a recommended dose of 10 µg/kg dose in the BMT setting (Schmitz et al, 1995; Stahel et al, 1994; Neupogen USPI). These studies demonstrated the safety and efficacy of the use of Neupogen as an adjunct to standard high-dose myeloablative chemotherapy for lymphoma (cyclophosphamide/etoposide/carmustine [CVB] or carmustine/etoposide/cytosine arabinoside/melphalan [BEAM]) and subsequent “rescue” with BMT in patients with Hodgkins disease or non-Hodgkins lymphoma receiving Neupogen 10, 20, or 30 µg/kg/day starting on day 1 after BMT (Schmitz et al, 1995; Stahel et al, 1994). A similar study in patients with leukemias, aplastic anemia, or lymphoma treated with conventional combinations of radiotherapy and chemotherapy (cyclophosphamide or busulfan) and subsequent BMT also demonstrated the safety and efficacy of filgrastim (Gran, 7 to 14 µg/kg/day) starting on day 5 after BMT (Kato et al, 1990; Masaoka et al, 1989). Neupogen statistically significantly reduced the duration of grade 4 neutropenia in these

phase 3 studies (Table 8). Neupogen also accelerated neutrophil recovery to $\geq 0.5 \times 10^9$/L and reduced the durations of fever and febrile neutropenia in these studies. In clinical trials, the reported adverse effects were those typically seen in patients receiving intensive chemotherapy followed by BMT.

Table 8. Effects of Neupogen on Neutropenia in Patients Undergoing High-dose Myeloablative Chemotherapy Followed by Autologous Bone Marrow Transplant (Randomized Controlled Phase 3 Clinical Trials)

Study	Tumor	Conditioning Chemotherapy/ Radiotherapy	Bone Marrow Transplant	Study Drug (Dose)	Median Duration of Grade 4 Neutropenia[e]		
					Low dose	High dose	Control
Schmitz et al (1995) N = 54	HD and NHL	CVB (HD patients); BEAM (NHL patients); No radiotherapy	Day 0; autologous bone marrow	Neupogen (10 or 30 µg/kg/day) Starting day 1 after BMT[b]	11 days (10 µg/kg/day)	13 days (30 µg/kg/day)	27 days P = 0.0001[e]
Stahel et al (1994) N = 43	HD and NHL	CVB; No radiotherapy	Day 0; autologous bone marrow	Neupogen (10 or 20 µg/kg/day) Starting day 1 after BMT[c]	10 days (10 µg/kg/day)	10 days (20 µg/kg/day)	21.5 days P < 0.0001[e]
Kato et al (1990) N = 70	ALL, AML, CML, aplastic anemia, lymphoma	Conventional combinations of radiotherapy, cyclo-phosphamide, or busulfan[a]	Day 0; allogeneic or syngeneic bone marrow	Gran (Kirin, Japan) (300 µg/m^2/day) (6.7 to 13.8 µg/kg/day) Starting day 5 after BMT[d]	15 days		19 days P < 0.001

ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; BCNU = carmustine (1,3-bis-[2-chloroethyl]-1-nitroso-urea); BMT = bone marrow transplant; CML = chronic myelogenous leukemia; HD = Hodgkins disease; NHL = non-Hodgkins lymphoma; BEAM = BCNU/etoposide/cytosine arabinoside/melphalan; CVB = cyclophosphamide/etoposide/BCNU;

[a] Including: cyclophosphamide with or without total body irradiation; total lymphoid irradiation; total abdominal irradiation; busulfan without radiotherapy; total body irradiation plus other chemotherapy

[b] Continuous IV infusion for 5 days, then adjusted as needed during ANC recovery for a scheduled maximum of 2 days.

[c] Continuous SC infusion for a maximum of 28 days. Once the ANC recovered to 1.0 x 10^9/L for 3 days, the dose was tapered to maintain ANC > 1.0 x 10^9/L

[d] 30-minute IV infusion, up to 14 days

[e] Control group compared with both Neupogen dose groups combined. No significant differences were seen between the two Neupogen dose groups for any endpoint.

6. Data on Radiation Exposure

6.1 Neupogen and Neulasta in Animal Radiation Models

Myelosuppression is one of the most common adverse effects of radiation therapy. Studies in mice, beagles, and rhesus monkeys have demonstrated accelerated hematopoietic regeneration and/or improved survival with the use of Neupogen or Neulasta after sublethal or lethal radiation (Table 9). Additional studies have been published assessing combinations of cytokines and various growth factors in animals exposed to radiation (details not described here) (Drouet et al, 2008; Hérodin et al, 2007; Farese et al, 2001; MacVittie et al, 2000; Coleman et al, 1998; Wagemaker et al, 1998; Neelis et al, 1997; Farese et al, 1996; MacVittie et al, 1996; Zeidler et al 1992; Waddick et al, 1991).

A study evaluating the effect of Neupogen and Neulasta on ANC recovery after irradiation and ABMT was conducted in monkeys. Male rhesus monkeys were myeloablated by TBI to 920 cGy on day 0 and then transfused with approximately 1×10^8 autologous bone marrow mononuclear cells per kilogram (Farese et al, 2003). On day 1 (approximately 20 hours after ABMT), monkeys were administered a single dose of Neulasta (100 or 300 µg/kg IV or SC), a single dose of Neupogen (300 µg/kg single dose IV or SC), or 0.1% autologous serum SC for 18 consecutive days. An additional group received daily doses of Neupogen (10 µg/kg/day SC) until ANC reached $\geq 3 \times 10^9$/L (12 to 17 days). A single SC dose of Neulasta was as effective as daily SC dosing of Neupogen in shortening the mean (SD) duration of severe (ANC $< 0.5 \times 10^9$/L) neutropenia (Neulasta 100 µg/kg, 4.0 [2.0] days; Neulasta 300 µg/kg, 2.3 [1.7] days; Neupogen 10 µg/kg/day, 6.0 [2.4] days; placebo, 11.2 [2.5] days) and improved the mean (SD) ANC at nadir (Neulasta 100 µg/kg, 0.301 [0.067] $\times 10^9$ cells/L; Neulasta 300 µg/kg, 0.398 [0.185] $\times 10^9$ cells/L; Neupogen 10 µg/kg/day, 0.135 [0.055] $\times 10^9$ cells/L; placebo, 0.063 [0.049] $\times 10^9$ cells/L). A single dose of Neupogen was not effective in this model. Pharmacokinetic data were determined from the IV cohorts. As expected, Neulasta exhibited lower clearance than Neupogen; therefore, the systemic exposure after IV administration of Neulasta was higher (Table 10). The clearance of Neulasta also was lower than that from normal monkeys; Neulasta was cleared from the circulation in approximately 2 days in normal monkeys but in approximately 8 days in the ABMT monkeys, which is likely due to a decrease in the neutrophil-mediated clearance secondary to the neutropenic condition.

Table 9. Effects of G-CSF on Radiation-induced Injury in Mice, Beagles, and Rhesus Monkeys

Author	Species	Radiation & Treatment	G-CSF Dose & Schedule	Key Results
Patchen et al, 1990	C3H/HeN mouse	Hematopoietic study: 650 cGy Survival study: 800 cGy	Filgrastim 2.5 µg/day SC on days 3-12, 1-12, or 0-12 after TBI	Filgrastim accelerated hematopoietic regeneration, enhanced survival, and was most effective when initiated 1 hr after TBI.
Plett et al, 2012	C57BL/6 mouse	~ 800 cGy ($LD_{70/30}$)	Filgrastim 125 µg/kg/day 24 hours after exposure to day 16	Filgrastim accelerated hematopoietic recovery and enhanced survival.
MacVittie et al, 1990	Beagle	200 cGy (sublethal) 350 cGy (LD_{60})	One day after TBI, filgrastim 10 µg/kg/day given SC for 14 days for the 200 cGy cohort or 21 days for the 350 cGy cohort	For a sublethal 200 cGy dose, filgrastim decreased the severity and shortened the duration of neutropenia and thrombocytopenia. For the lethal 350 cGy dose, filgrastim markedly reduced the lethality to zero.
Schuening et al, 1989	Beagle	400 cGy	100 µg/kg filgrastim given SC BID for 21 days or until death, beginning either 2 hours or 7 days after TBI	4 of 5 dogs that started filgrastim treatment within 2 hours after TBI showed complete and sustained endogenous hematopoietic recovery, while all 5 dogs that started treatment on day 7 after TBI died between days 17 and 20.
MacVittie et al, 2005	Beagle	350-800 cGy	10 µg/kg filgrastim, QD beginning 1 day after TBI until ANC ≥ 2000/µL	Filgrastim reduced duration of neutropenia and improved survival in animals receiving ≤ 600 cGy.
Yu et al, 2011	Beagle	230 cGy mixed fission neutron-γ irradiation (LD_{40})	10 µg/kg/day for 21 days starting 1 hour post radiation	Improved survival, decreased neutrophil nadir, and decreased duration of neutropenia

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ANC = absolute neutrophil count; BID = twice daily; QD = daily; cGy = centiGrays; DSN = duration of severe neutropenia; G-CSF = granulocyte colony-stimulating factor; IV = intravenous; $LD_{x/y}$ = lethal dose for x% of animals by day y; SC = subcutaneous; TBI = total body irradiation

Table 9. Effects of G-CSF on Radiation-induced Injury in Mice, Beagles, and Rhesus Monkeys

Author	Species	Radiation & Treatment	G-CSF Dose & Schedule	Key Results
Farese et al, 1996	Rhesus monkey	700 cGy	One day after TBI, filgrastim 10 µg/kg/day for 21-23 days	Daily administration of filgrastim decreased the mean DSN from 15.5 days to 12.3 days.
Farese et al, 2012	Rhesus monkey	600 cGy TBI ($LD_{10/30}$, with supportive care administration)	Filgrastim 10 µg/kg/day, daily through neutrophil recovery, starting on day 1 or pegfilgrastim 300 µg/kg on day 1 or day 1 and 7 post-exposure	Filgrastim and pegfilgrastim improved the speed of hematopoietic recovery after TBI. Administration of pegfilgrastim on days 1 and 7 was most effective in this study.
Farese et al, 2013	Rhesus monkey	750 cGy TBI ($LD_{50/60}$)	Filgrastim 10 µg/kg/day, daily through neutrophil recovery, starting on day 1	Filgrastim reduced 60 day mortality and decreased duration of neutropenia compared to controls.

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ANC = absolute neutrophil count; BID = twice daily; QD = daily; cGy = centiGrays; DSN = duration of severe neutropenia; G-CSF = granulocyte colony-stimulating factor; IV = intravenous; $LD_{x/y}$ = lethal dose for x% of animals by day y; SC = subcutaneous; TBI = total body irradiation

Table 10. Pharmacokinetic Mean (SD) Values in Rhesus Monkeys After IV Administration of Neulasta or Neupogen on Day 1 After Irradiation and Autologous Bone Marrow Transplant

Parameter	Neulasta 100 µg/kg	Neulasta 300 µg/kg	Neupogen 300 µg/kg
n	4	4	4
C_{max} (ng/mL)	2,200 (310)	6,180 (480)	3,570 (990)
T_{max} (hr)	1.19 (0.94)	0.44 (0.38)	0.31 (0.13)
$t_{½}$ (hr)	22.2 (4.6)	16.1 (4.4)	4.7 (2.1)
$AUC_{(0\text{-last})}$ (ng·hr/mL)	46,300 (9,200)	171,000 (31,000)	6,340 (940)
CL (mL/hr/kg)	2.22 (0.44)	1.80 (0.32)	47.9 (6.50)
V_c (mL/kg)	46.2 (6.5)	48.8 (3.9)	89.5 (26.1)

Adapted from: Farese et al, 2003

$AUC_{(0\text{-last})}$ = area under the concentration-time curve from time 0 to the time of the last detectable concentration; CL = serum clearance after IV administration; C_{max} = maximum observed concentration; IV = intravenous; n = number of animals; $t_{1/2}$ = half-life associated with the terminal phase; T_{max} = time at which maximum concentration was observed; V_c volume at the central compartment

6.2 Case Studies of Human Exposure to Radiation

Colony-stimulating factors and other growth factors can potentially improve chances of survival in victims of myelosuppression after exposures to radiation by stimulating the residual progenitor cells to produce neutrophils and have been used for this purpose. Data from people who have been treated with CSFs after being exposed to various doses of radiation from radiation accidents are available from a few published analyses and are discussed below. The specific G-CSF product was not always clearly identified.

After the Chernobyl nuclear accident in April 1986, hematopoietic growth factor administration with or without BMT was proposed for treating pancytopenia due to radiation exposure, and various cytokines have been shown in studies in animals and in case studies in humans to stimulate growth of remaining or residual post-exposure neutrophils and platelets (Hérodin and Drouet, 2005; Thierry et al, 1995). A few publications reporting case studies on the use of various growth factors in a small number of cases following radiation emergencies are available, as summarized below.

In an inventory of growth factor use in 38 victims of radiation accidents in various countries from 1987 to 2000 with estimated global doses of radiation varying between 80 and > 1000 cGy, 25 victims were recorded to have received G-CSF either as the only growth factor (N = 12), in combination with granulocyte monocyte colony-stimulating factor (GM-CSF) (N = 10), or in combination with epoetin (EPO) and macrophage growth and development factor (MGDF) (N = 3); additional victims received GM-CSF as the only growth factor (N = 11) or in combination with interleukin-3 (IL-3; N = 2). A total of 20 of the 25 victims treated with G-CSF were reported to have survived the respective incident. This included all of the 12 who received G-CSF as the only growth factor (after estimated 100 to 400 cGy exposure [Istanbul, Turkey 1998] or 350 to 400 cGy exposure [Meet-Halfa, Egypt 2000]); 7 of the 10 who received G-CSF in combination with GM-CSF (after estimated 200 to > 600 cGy exposure [Samut Prakarn, Thailand 2000] or < 350 cGy exposure [Gilan, Iran 1996]), and 1 of the 3 who received G-CSF in combination with EPO and MGDF (after estimated 80 to 550 cGy [neutron] or 130 to 850 cGy [gamma] exposure [Tokai-Mura, Japan 1999]) (Hérodin and Drouet, 2005). G-CSF doses and durations used in these incidents were as follows: Istanbul, 5 to 8 µg/kg/day for 6 to 12 days; Meet-Halfa, 10 µg/kg/day, late and prolonged administration; Samut Prakarn, 5-20 µg/kg/day, late administration after day 17 over 6 to 28 days; Gilan, 300 µg/day for 10 days (Hérodin and Drouet, 2005). After the Tokai-Mura incident, 2 victims received G-CSF 100 µg/day from day 1 postexposure to stem cell

transplantation on day 6 or day 9, and the victim who survived the incident received G-CSF 100 µg/day from day 2 to 28 and a BMT on day 4; the latter victim's neutrophils recovered before day 28 following a nadir of 1.1 x 10^9/L on day 20 (Hérodin and Drouet, 2005; Hirama et al, 2003).

After a radiation accident in Istanbul, Neupogen (8 µg/kg/day) was administered for 9 consecutive days to a 10-year old victim, starting approximately 4 weeks after exposure when the neutrophil count was < 1.0 x 10^9/L. The neutrophil count recovered to normal levels after 9 days of Neupogen.

A review of the available case information recorded in the Radiation Emergency Assistance Center/Training Site (REAC/TS) registry (Oak Ridge, Tennessee), showed that 25 of 28 exposure victims identified as having received CSFs after radiation accidents appeared to have faster neutrophil recovery compared with other subjects recorded in the registry. Most of these 25 patients received G-CSF and GM-CSF concurrently for significant periods; some patients also received IL-3 (Waselenko et al, 2004).

No conclusions regarding the use of Neupogen or G-CSFs in general in this setting can be drawn from the currently available reports describing a very small number of cases. Additional limitations of these case studies include the variable radiation doses; use of growth factors other than CSFs; and large variability in the CSF dose, time of starting dose, and duration of CSF use. In many cases CSFs were not initiated until weeks after the incident. The case studies reviewed above were not sponsored by Amgen, and in most cases the actual G-CSF product used is not clear from available literature. Despite limitations, information described in these case studies would not preclude the use of CSFs in accidental radiation exposure.

6.3 Clinical Trials

Clinical trials conducted in the setting of patients with cancer receiving radiation therapy have typically been conducted in a small number of subjects, and no CSF is currently approved in this indication.

In a small clinical study of Neupogen in radiation therapy, 7 patients with Hodgkin's disease received daily SC injections of Neupogen during large field subdiaphragmatic irradiation (3550 to 4320 cGy over 5 to 6 weeks) after thoracic mantle fields (4320 to 4500 cGy over 5 to 6 weeks) (Knox et al, 1994). Compared to historical controls, Neupogen (3 µg/kg/day during the 5 to 6 weeks of subdiaphragmatic irradiation)

statistically significantly increased the WBC and ANC throughout the period of subdiaphragmatic irradiation. Mean nadir WBC (5.98 x 10^9/L) and ANC (4.71 x 10^9/L) in the Neupogen group were approximately twice those of historical controls (3.32 x 10^9/L and 2.39 x 10^9/L, respectively; $P < 0.002$). Three of the 7 patients reported mild musculoskeletal pain, but there was no other apparent toxicity. Other published studies have also shown filgrastim to be effective for treatment of neutropenia during craniospinal irradiation or external beam irradiation therapy (MacManus et al, 1993; Fushiki et al, 1989).

7. Conclusions

The effectiveness of Neupogen and Neulasta is established in the setting of chemotherapy-induced neutropenia, and for Neupogen across multiple indications. Approved indications that are potentially relevant to the setting of ARS-HS include use in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy alone (for both drugs) or with subsequent BMT (for Neupogen only). The use of Neupogen and Neulasta is based on the established biologic mechanism of G-CSFs, which stimulate neutrophil production, accelerate neutrophil recovery, and reduce the severity and duration of febrile neutropenia and the incidence of infections.

Nonclinical data from studies in mice, beagles, and monkeys demonstrate reduced severity of myelosuppression with enhanced neutrophil recovery and improved survival after G-CSF treatment of animals exposed to lethal and sublethal doses of radiation.

Limited clinical trial and case study data are available in the literature regarding Neupogen administration in persons exposed to radiation; however, no conclusions can be drawn from this information.

Based on the underlying biology and limited animal studies, Amgen considers that Neupogen and Neulasta have the potential to provide clinical benefit as treatments for radiation-induced myelosuppression resulting from accidental radiation exposure.

8. References

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